RESEARCH ARTICLE

Investigating associations between urinary phthalate metabolite concentrations and chronic diarrhea: findings from the National Health and Nutrition Examination Survey, 2005–2010

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Abstract

This study aimed to explore the relationship between chronic diarrhea and urinary phthalate metabolite concentrations in US adults from the 2005–2010 NHANES study. After adjusting for potential confounding factors, logistic regression was used to explore the relationship between phthalates (PAEs) concentrations and chronic diarrhea, Bayesian kernel machine regression (BKMR), and quantile g calculation (quantile-based g calculation, qgcomp) which was used to study the combined and independent effects of PAEs on gastrointestinal infections. In the current study, 4260 adult participants over the age of 20 from the NHANES study were included, of whom 542 (12.72%) were assessed as having chronic diarrhea. In multivariate logistic regression analysis, after adjusting for all relevant covariates, the results showed that urinary phthalate metabolite concentrations were significantly associated with the risk of chronic diarrhea ($P<0.001$). Various PAEs were risk factors for chronic diarrhea, among which MiBP (OR=1.419, 95% CI: 1.416–1.423) and MCPP (OR=1.237, 95% CI: 1.235–1.239) were more significant. The BKME results showed a significant increase in the risk of chronic diarrhea with increasing total levels of the PAEs mixture. Mixed exposure to PAEs can promote the occurrence of chronic diarrhea, and the effect was more pronounced in obese people. Notably, most PAEs showed some degree of protection in overweight people. The risk effect of PAEs was more significant in the middle-aged and older population than in the younger population.

Keywords Phthalate metabolite · Chronic diarrhea · NHANES · Bayesian kernel machine regression · Quantile g-computation

Introduction

Despite the increasing harmfulness of phthalates and their metabolites, owing to their low cost, appealing properties, and absence of suitable alternatives, phthalates are utilized in plastics as plasticizers and in countless consumers. Large-scale

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use as an additive in products continues (Wang et al. 2021). Globally, few epidemiological or clinical human researches have revealed that phthalates (PAEs) pose a prominent ecological risk due to their multiple toxicity potential and ubiquitous detection in the environment (Hamid et al. 2020). Human ingests more than a dozen phthalates and their metabolites by passive ingestion from breathed air, general environment, food, beverages, and everyday household products that can result in a variety of functional impairments, comprising health hazards to adolescents and children, epigenetic regulation, male and female reproductive toxicity, overweight and obesity, type II diabetes and insulin resistance, skeletal deformities, etc. (Benjamin et al. 2017). PAEs are a typical class of endocrine disruptors that can accumulate in organisms and interfere with their secretion systems (Zhu et al. 2022). An increasing number of studies have investigated how endocrine-disrupting chemicals (EDCs) affect the gut microbiota of a range of animals, and resident bacteria in the gut and other parts of the body can greatly influence the host response (Rosenfeld 2021).

The intestine is an important digestive organ and the largest immune organ in the human body (Guo et al. 2021). Intestinal homeostasis is the dynamic balance of interactions between the host's intestinal mucosa, immune barrier, gut microbiome, nutrients, and metabolites. Once homeostasis is out of balance, it increases the risk of intestinal disease (Shen et al. 2022). Chronic diarrhea is a prevalently presenting symptom in both primary care and specialist gastroenterology departments. Over 5% of the global population is believed to suffer from chronic diarrhea. (Alonso-Cotoner et al. 2021). Diarrhea is the main pathological feature of inflammatory bowel disease, and the expression and function of major intestinal ion transporters are significantly reduced (Jayawardena et al. 2020). Recently, some research evidence has shown that exposure to DEHP contamination significantly increases intestinal permeability and enhances intestinal inflammation (Deng et al. 2020).

Inflammatory dysregulation is a common thread connecting the most important chronic diseases and conditions in all physiological systems and associated comorbid conditions (Dietert 2012). As a common chronic disease, chronic diarrhea is closely related to inflammation, and some studies have shown that exposure to EDCs can increase inflammation in certain populations (Zota et al. 2018). The relationship between EDCs and inflammatory bowel diseases such as chronic diarrhea has also attracted more and more attention, but as typical EDCs, there are few studies on the relationship between EDCs and intestinal diseases. Hence, this study's objective was to evaluate if variations in phthalate exposure, as estimated by urine concentrations, were related to variations in chronic diarrheal disease in US adults samples.

Methods

Study population

The National Health and Nutrition Examination Survey (NHANES) is a biennial cross-sectional survey that is utilized for evaluating the health and nutritional status of children and adults in the USA (Zand et al. 2015). NHANES, a critical program of the National Center for Health Statistics (NCHS), guarantees that participants are selected from diverse geographic and racial/ethnic groups, thus providing a representative sample total population of the USA. For complete information on the data provided by NHANES and precise details of data collection, please refer to its specific website (http://www.cdc.gov/nchs/nhanes.htm). Data pooled in the study from participants during the 2005–2006, 2007–2008, and 2009–2010 NHANES surveys, excluding individuals with (1) incomplete gut health questionnaire assessment data, (2) colon cancer and/or rectal cancer, (3)

lack of baseline status, and (4) population under 20 years of age. The final analysis of chronic diarrhea comprised 4260 patients aged 20 years and older (2117 males and 2143 females) (Fig. 1). Additionally, weighted estimates were established and extrapolated to sample data to get nationwide estimates.

Exposure assessment and outcome assessment

For analysis, urine specimens were stored, processed, and transported to the Department of Laboratory Sciences, the National Center for Environmental Health, and the Centers for Disease Control and Prevention. The vials were kept under proper freezing (20°C) until they were transported to the National Center for Environmental Health for testing. The following phthalate metabolites were detected in urine utilizing high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS). NHANES was replaced for every chemical concentration below the limit of detection (LOD) by dividing the LOD value by the square root of 2. Environmental pollution exposures include mono-2-ethyl-5-carboxypentyl phthalate (MECPP), mono(carboxynonyl) phthalate (MCNP), mono-benzyl phthalate (MBzP), mono-(3-carboxypropyl) phthalate (MCPP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(carboxyoctyl) phthalate (MCOP), mono-n-butyl phthalate (DCHP), mono-ethyl phthalate (MEP), mono-(2-ethyl)-hexyl phthalate (MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-isobutyl phthalate(MiBP).

The BSFS and frequency criteria were utilized for the evaluation of chronic constipation, both from the Gut Health Questionnaire, a gender-related standardized question panel. The BSFS utilized a colored picture card with textual descriptions and pictures of seven stool types and provided them to recipients. The following written question was asked: "Look at this card and tell me which stool type resembles your normal or commonest stool type." Diarrhea was identified as type 6 (fluffy, flaky, mushy stools, and rough edges) or type 7 (water sample, no solid flakes). Bowel function is also measured by the bowel movements frequency per week and answers the question: "How often do you normally experience bowel movements per week?" According to previous data from NHANES, it is less than 3 times (constipation), 3–21 times (normal), and exceed 21 times (diarrhea).

Covariates

According to previous studies, multiple potential variables were included in multivariate models confounding the relation between urine phthalate metabolite concentrations and chronic diarrhea, including sex (male/female), age (20–35,
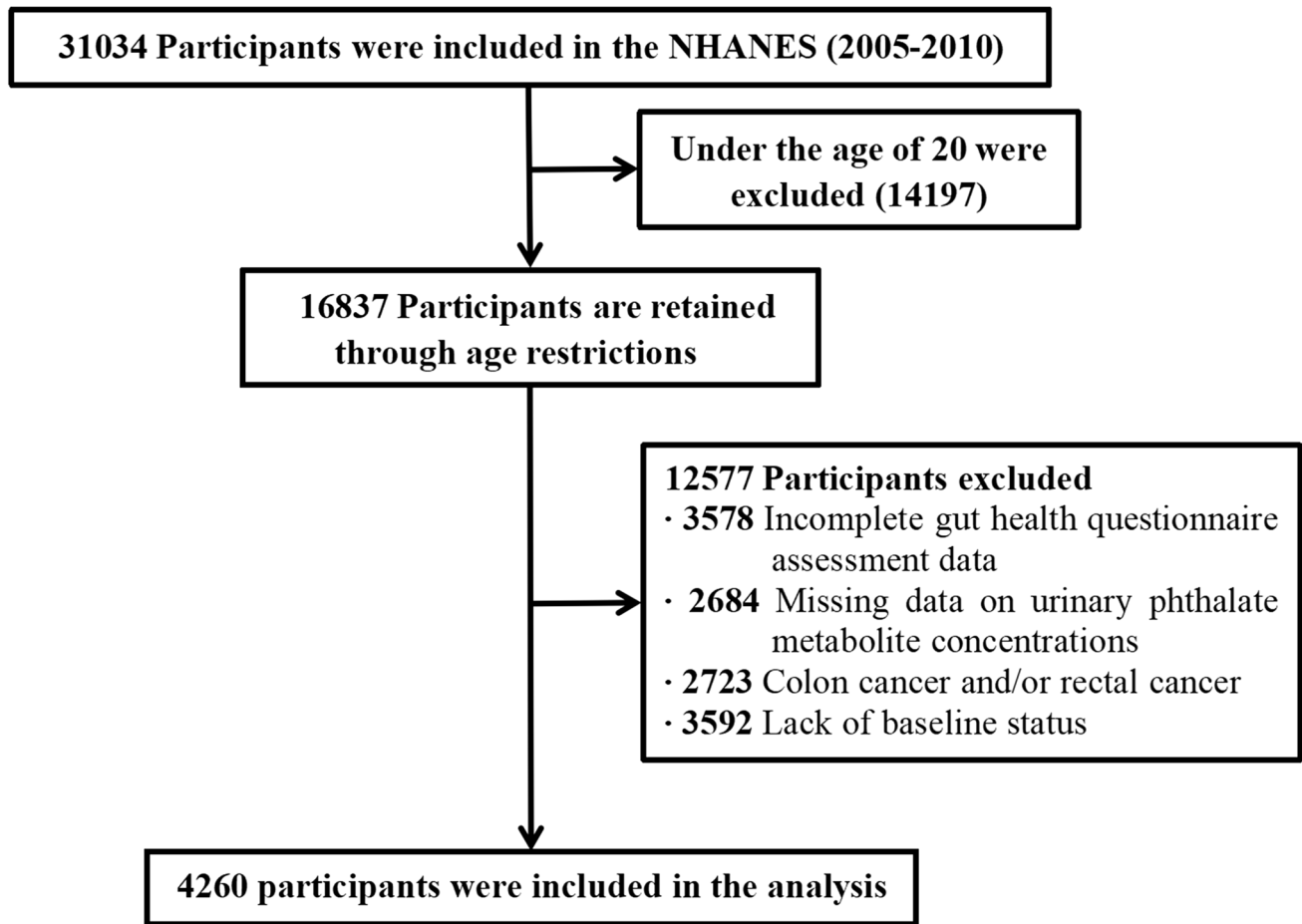
Fig. 1 Selection process of subjects.

36–45, 46–55, 56, and older), race/ethnicity(Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other/multi-racial), body mass index (BMI) category, poverty income ratio (PIR, continuous), creatinine, marital status (married, divorced/widowed/separated, never married, living with partner), and education (less than 9th grade, 9th–11th grade, high school grad/GED or equivalent, some college or AA degree, college grad, or above). In the current study, we defined BMI as three levels: <25.00 (underweight/normal weight), 25.00–30.00 (overweight), and >30.00 (obese). The PIR is estimated by dividing the household income (relied on the poverty criteria specific to household size) by the year and state for indicating the participant's socioeconomic status within the family.

Statistical analysis

All PAEs and associated covariates distributions were evaluated. PAEs and other continuous covariates were reported as interquartile and medians ranges. Other categorical covariates are number and percentage. For additional model analysis, all concentrations of PAEs were natural log (ln) transformed. The chi-square test (categorical variables) or Wilcoxon rank-sum test (skewed distribution) were utilized for assessing variations in PAEs and covariates between the diarrhea and non-diarrhea groups. For investigating pairwise correlations between raw PFAS values, Spearman rank correlation analysis was utilized. Prior to regression analysis, missing values for covariates were imputed utilizing multiple imputations of the fully conditional normative (FCS-MI) method. This method enables the specification of multivariate imputation models on a variable-by-variable basis and gives a principled but malleable approach for addressing missing data. Ten datasets were established and modeled individually with missing data imputation. The results in single contaminant and exposure analyses of mixtures of PAEs were aggregated for obtaining final impact parameters. Logistic regression models were utilized for evaluating the relation between PAEs and chronic diarrhea. PAEs homologues associated with chronic diarrhea were analyzed one at a time. Variance inflation factor (VIF) values and tolerance are calculated for evaluating multicollinearity among covariables, with tolerances <0.1 and VIF > 10

indicating multicollinearity. For education, sex, marital status, BMI, age, poverty income ratio, race, and creatinine concentration, all models were adjusted. In our regression model, MINP, MnOP, MMP, and MCHP were not incorporated owing to their low detection rate.

The individual and overall impacts of PAEs on the chronic diarrhea incidence were estimated utilizing Bayesian kernel machine regression (BKMR). BKMR is a statistical method that can flexibly model the combined effects of pollutant mixtures and can be used to estimate the effects of individual mixture components, the effects of overall mixture components, and the interactions between mixture components. Fitting exposure-response relationships for binary outcomes using a probabilistic link function. The core of the BKMR model is kernel machine regression (KMR), which iteratively regresses the exposure-response function using a Gaussian kernel function. PAEs were ln-transformed, centered at 0, and scaled using standard deviation 1 for all BKMR analyses to account for skewness and minimize the extreme values effects and various value scales within the variable. As previously stated, for the corresponding covariates, each BKMR model was adjusted. The overall mixed PAEs effect was assessed by subtracting the mean of the results at the 25th percentile for all PAEs at the 75th percentile by subtracting the mean of the results at the 75th percentile for all PAEs. Likewise, individual effects of every PAEs mixture component were calculated by subtracting the mean outcome value when the provided PAEs were at their 25th percentile minus provided PAEs at their 75th percentile while keeping other PAEs homologues fixed at their median unchanged. Plots were utilized for analyzing the overall association of a PAEs mixture with several measures of glucose homeostasis and for demonstrating the exposure-response relation for every PAE isoform, whereas maintaining other exposures at their 50% percentile and covariates constant.

Though BKMR benefits from exposure-response function modeling's flexibility and permits for nonlinear and non-additive associations between several PAEs and chronic diarrhea, it lacks concise parametric reasoning (e.g., single coefficient of change in results). Additionally, depending on parametric inference, we utilize a newly developed quantile-based g calculation approach for exploring joint effects. Quantile g calculation is a parameter-based, generalized linear model-based implementation of g-computation used to estimate the change in quantile results while increasing all exposures in a particular mixture. This method comprises weighted quantile regression (WQS) inference simplicity with g-computation flexibility, whereas accounting for BKMR's nonlinearity and non-additivity resulting in lower bias and more robustness. SAS V9.4 (SAS Institute Inc., Cary, NC, USA) and R (version 3.6.1, R Development Core Team 2019) were utilized for conducting all statistical analyses. A α level of 5% (two-sided) was deemed statistically significant.

Results

Population characteristics

Table 1 illustrates the demographic characteristics of the overall population enrolled in the study. In the current study, 4260 adult participants over the age of 20 from the NHANES study were included, of whom 542 (12.72%) were assessed as having chronic diarrhea. The ages of the participants were mainly distributed between 20 and 35 years old and 56 years old and above. Moreover, the obesity group accounted for a higher proportion (43.7%) in the chronic diarrhea population. Most subjects were non-Hispanic white. Between the chronic diarrhea group and the normal group, there were significant variations in age, BMI, PIR, and education level ($P<0.05$).

Urinary phthalate metabolites

Ten of the eleven phthalate metabolites investigated in this study were observed in over 92% of the study population, while one was observed in over 69% of the population (Table 2). The detection frequencies of most phthalate metabolites were roughly similar except for mono-ethyl phthalate (MEP) and mono-isobutyl phthalate (MiBP). The difference between the normal and diarrhea groups was statistically significant ($P<0.05$). Pairwise correlation analysis showed that some of the PAEs metabolites had significant correlations. For different PAEs, correlation coefficients varied from 0 to 0.97, with strong correlations among several PAEs metabolites (MEHP, MEHHP, MEOHP, and MECPP) (Fig. 2).

The relationship urinary phthalate metabolite concentrations and chronic diarrhea

The relation between different PAEs types and the risk of chronic diarrhea is illustrated in Table 3. In multivariate logistic regression analysis, after adjusting for all relevant covariates, the results showed that urinary phthalate metabolite concentrations were significantly associated with the risk of chronic diarrhea ($P<0.001$). The risk of chronic diarrhea increases with increasing concentrations of PAEs. Various PAEs were risk factors for chronic diarrhea, among which MiBP (OR=1.419, 95% CI: 1.416–1.423) and MCPP (OR=1.237, 95% CI: 1.235–1.239) were more significant, whereas MCNP, MEHP, and MEOHP are protective factors for chronic diarrhea (Supplementary Fig. 1). For further exploring the specific correlation between the various phthalate metabolites concentrations and chronic diarrhea, we performed a subgroup analysis based on BMI and age, and the results showed (Supplementary Table 1) that in

Table 1 Baseline characteristics of the 4260 participants

Characteristic	Frequency (%) or median (IQR)		P value
	Normal (*n*=3718)	Chronic diarrhea (*n*=542)	
Age (years)			0.004
20–35	1089 (29.3)	122 (22.5)	
36–45	656 (17.6)	102 (18.8)	
46–55	643 (17.3)	90 (16.6)	
56 and older	1330 (35.8)	228 (42.1)	
Gender			0.975
Male	1848 (49.7)	269 (49.6)	
Female	1870 (50.3)	273 (50.4)	
Marital status			0.697
Married	2031 (54.6)	299 (55.2)	
Divorced, widowed, separated	789 (21.2)	121 (22.3)	
Never married	608 (16.4)	87 (16.1)	
Living with partner	290 (7.8)	35 (6.4)	
BMI(kg/m2)			0.001
<25.00 (underweight/normal weight)	1096 (29.5)	126 (23.2)	
25.00–30.00 (overweight)	1283 (34.5)	179 (33.1)	
>30.00 (obese)	1339 (36.0)	237 (43.7)	
Poverty income ratio (PIR)			0.001
	2.25 (1.17–4.31)	1.87 (1.02–3.77)	
Education			<0.001
Less than 9th grade	366 (9.8)	82 (15.1)	
9th–11th grade	573 (15.4)	110 (20.3)	
High School grad/GED or equivalent	942 (25.3)	132 (24.4)	
Some college or AA degree	1050 (28.2)	120 (22.1)	
College Grad or Above	787 (21.3)	98 (18.1)	
Race/ethnicity			0.154
Mexican American	653 (17.6)	107 (19.7)	
Other Hispanic	265 (7.1)	49 (9.1)	
Non-Hispanic White	1906 (51.3)	249 (45.9)	
Non-Hispanic Black	740 (19.9)	115 (21.2)	
Other/multi-racial	154 (4.1)	22 (4.1)	
Creatinine, urine (mg/dL)			
	115.00 (66.00–169.00)	114.00 (68.00–170.25)	0.938

Table 2 Concentration distribution of phthalate metabolites in different groups

Phthalates	Detectable rate (%)	Median (IQR)		P value
		Normal (*n*=3718)	Chronic diarrhea (*n*=542)	
Mono(carboxynonyl) phthalate (MCNP)	92.2	2.50 (1.22–4.90)	2.58 (1.18–5.40)	0.135
Mono(carboxyoctyl) phthalate (MCOP)	96.6	6.20 (2.90–16.40)	7.50 (3.10–14.64)	0.922
Mono-n-butyl phthalate (DCHP)	99.2	16.70 (8.16–32.10)	19.10 (9.10–35.70)	0.086
Mono-ethyl phthalate (MEP)	99.8	80.26 (29.69–234.10)	97.57 (37.42–287.10)	0.023
Mono-(2-ethyl)-hexyl phthalate (MEHP)	69.0	1.90 (0.85–4.90)	1.80 (0.78–4.20)	0.246
Mono-benzyl phthalate (MBzP)	98.0	6.78 (2.81–14.80)	6.67 (3.20–17.24)	0.073
Mono-(3-carboxypropyl) phthalate (MCPP)	96.6	2.30 (1.10–4.79)	2.60 (1.20–5.00)	0.370
Mono-(2-ethyl-5-hydroxhexyl) phthalate (MEHHP)	99.5	16.80 (7.43–39.80)	17.77 (8.99–38.00)	0.348
Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)	98.6	10.10 (4.60–22.85)	10.80 (5.10–22.20)	0.599
Mono-isobutyl phthalate (MiBP)	97.8	6.40 (3.00–12.60)	7.70 (3.60–14.47)	0.003
Mono-2-ethyl-5-carboxypentyl phthalate (MECPP)	99.9	24.99 (11.91–54.50)	28.90 (13.40–58.80)	0.320

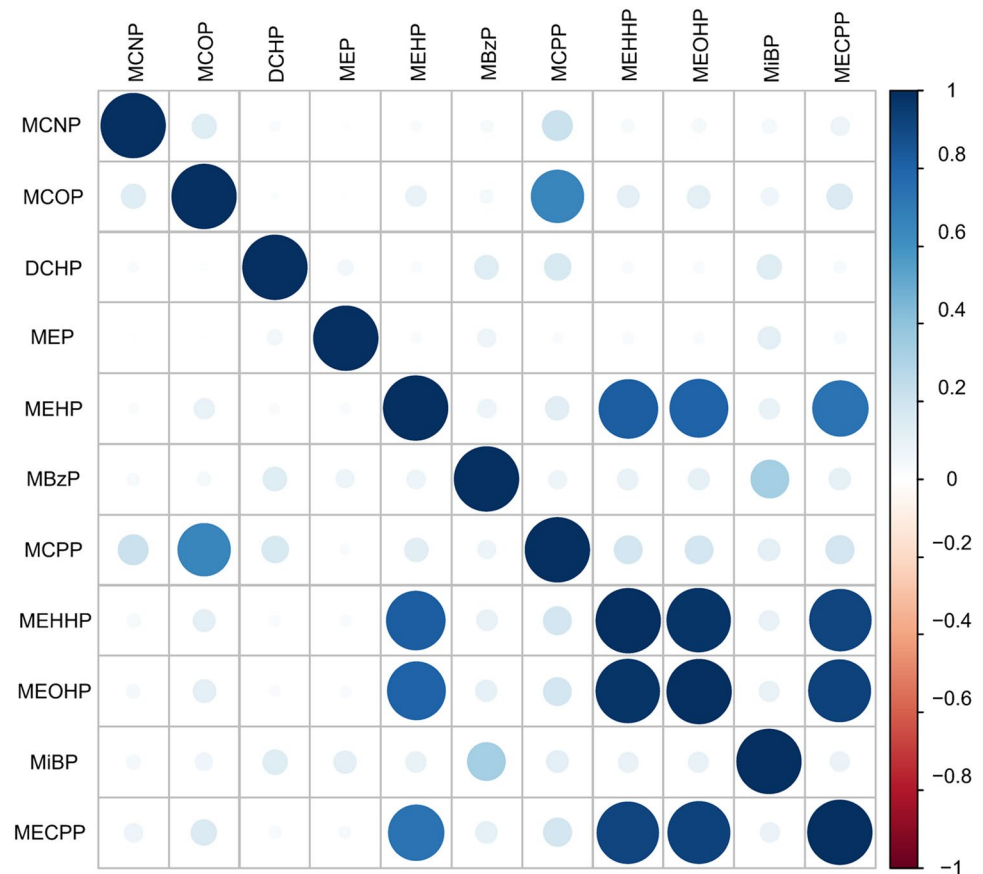**Fig. 2** Spearman correlations between different phthalate metabolites.

Table 3 Logistic regression results of the association of different phthalate metabolites with chronic diarrhea

Phthalates	OR (95%CI)	*P* value
Mono(carboxynonyl) phthalate (MCNP)	1.099 (1.097–1.102)	<0.001
Mono(carboxyoctyl) phthalate (MCOP)	1.034 (1.032–1.035)	<0.001
Mono-n-butyl phthalate (DCHP)	1.195 (1.192–1.198)	<0.001
Mono-ethyl phthalate (MEP)	1.114 (1.112–1.115)	<0.001
Mono-(2-ethyl)-hexyl phthalate (MEHP)	0.892 (0.890–0.893)	<0.001
Mono-benzyl phthalate (MBzP)	1.136 (1.134–1.138)	<0.001
Mono-(3-carboxypropyl) phthalate (MCPP)	1.237 (1.235–1.239)	<0.001
Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)	1.020 (1.018–1.022)	<0.001
Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)	0.975 (0.974–0.977)	<0.001
Mono-isobutyl phthalate (MiBP)	1.419 (1.416–1.423)	<0.001
Mono-2-ethyl-5-carboxypentyl phthalate (MECPP)	1.128 (1.126–1.130)	<0.001

Model was adjusted for age and gender, race/ethnicity, education, poverty income ratio (PIR), marital status, body mass index, and creatinine

the obese population, various PAEs were risk factors for chronic diarrhea ($P<0.001$). In overweight people, most PAEs showed some degree of protection (Supplementary Table 2). The risk effect of PAEs was more significant in the middle-aged and elderly population (>46) compared with the younger population (<46). The risk effect of MCPP on chronic diarrhea in the 46–55 age group (OR=2.308, 95% CI: 2.299–2.318) was more than double that of the 20–35 age group (OR=1.189, 95% CI: 1.185–1.194).

PAEs joint and individual exposure with chronic diarrhea based on BKMR

Figure 3 A illustrates the overall association between PAEs mixture and chronic diarrhea. The risk of chronic diarrhea

elevated significantly as the total mixture of PAE levels elevated. Additionally, we evaluated the individual exposure-response function of PAEs and chronic diarrhea (Fig. 3C). Changes from 25 to 75% in MECPP, MEHHP, and DCHP were associated with an increased risk of chronic diarrhea (Fig. 3B). MCOP, MiBP, and MCPP exposure were positively correlated with an increased risk of chronic diarrhea. There was no interaction between different PAEs (Fig. 3D).

Sensitivity analysis

In the content of sensitivity analysis, the results of the analysis based on quantile g calculations were used to assess the robustness and stability of the BKMR and multivariate logistic regression modeling results. Combined effects analysis showed that mixed exposure to PAEs contributed to the increased risk of chronic diarrhea. MECPP had the largest

positive weight, indicating a greater association with chronic diarrhea. At the same time, by comparing the results of the regression data before and after weighting, it was found that the data results before and after weighting are consistent (Supplementary Table 3).

Discussion

According to some studies, adults have a prevalence of chronic diarrhea ranging from 1 to 5%. (Burgers et al. 2020). Common causes include inflammation, tumors, malabsorption, infection, vascular and irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD). Other causes include food intolerances, medications side effects, or post-operative conditions. Additionally,
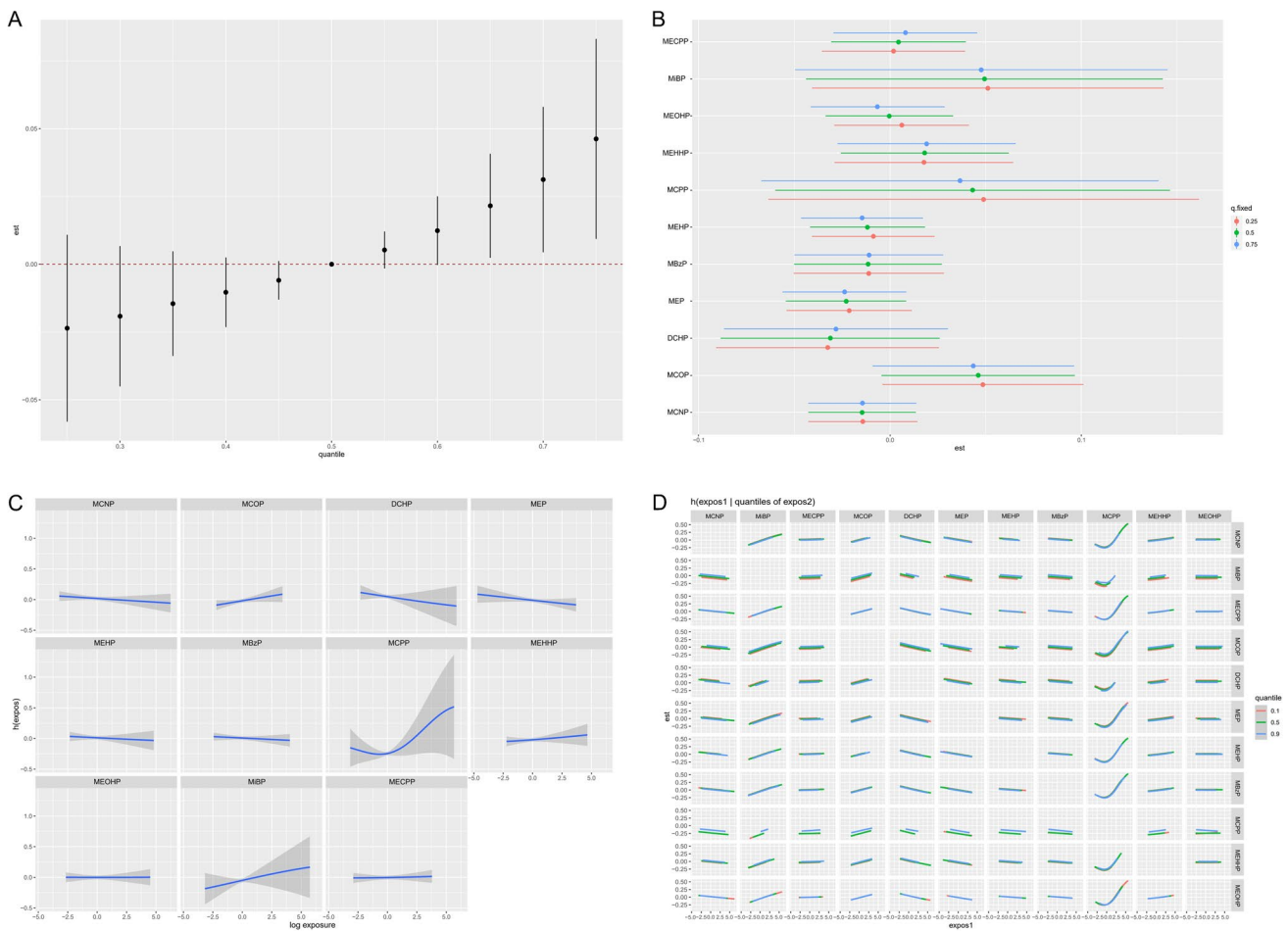

Fig. 3 The association between phthalate metabolites and chronic diarrhea in adults was studied utilizing the BKMR model. The model is based on age and gender, race/ethnicity, education, poverty income ratio (PIR), marital status, body mass index, and creatinine. **A** Cumulative effects of phthalate metabolites (estimates and 95% confidence intervals). **B** Univariate response functions for every phtha-

late metabolite have 95% confidence bands, and other metabolites are fixed at the median. **C** Single phthalate metabolite effect (estimated value and 95% confidence interval). **D** Bivariate exposure-response function for every of the two phthalate metabolites among patients with chronic diarrhea.

diarrhea can be a symptom of systemic disorders, such as hyperthyroidism or diabetes (Hammer 2021).

One of the major causes of global disease burden is thought to be ambient air pollution. The association of air pollution with respiratory and cardiovascular disease was first recognized, and then accumulated data suggested that the gut may also be compromised (Vignal et al. 2021). PAEs (phthalates) are commonly utilized in industrial production to soften hard plastics (plasticizers), and their related products are widely distributed in our everyday lives as emerging pollutants. As PAEs are not chemically bonded to the product, they are easily transported to the surrounding environment (Xiong and Pei 2021). However, the research between PAEs and intestinal health is very scarce. The BKMR results of this study indicated that the overall effect of mixed exposure to PAEs promoted the occurrence and development of chronic diarrhea to a certain extent. Studies have shown that the accumulation of PAEs in the liver and intestines was significantly increased in mice exposed to PAEs pollution (Deng et al. 2021). Endocrine disrupting chemicals/mixtures (EDCs) are chemicals that disrupt hormone homeostasis in the body. They are critical in the function of the endocrine system, including the hypothalamic-pituitary-gonadal axis (HPG axis). Some common and widely studied EDCs have negative effects on the endocrine system and a wide range of activities including PAEs (Czarnywojtek et al. 2021). Exposure to EDCs was strongly associated with dysregulated inflammatory responses, and exposure to PAEs was positively associated with both pro- and anti-inflammatory markers. These findings underscore the impact of EDCs on the regulation of inflammation, which may be closely related to a range of chronic diseases (Liu et al. 2022), while there is evidence that PAE exposure is associated with oxidative stress, adiponectin, and inflammatory cytokines in diabetic patients (Duan et al. 2017). In neonates, phthalate-mediated PPAR-γ inhibition by neutrophils is more sensitive, which may be related to a decrease in anti-inflammatory signaling (Vetrano et al. 2010). Results from animal studies indicate that certain phthalates can affect immune and inflammatory function in rodents when administered at appropriate doses and by appropriate routes, but no consistent pattern has emerged. Results range from enhanced immune or inflammatory responses to no effect, suppressive, or immunosuppressive activity (Kimber and Dearman 2010). Interestingly, an important role for phthalates in promoting inflammation was not supported in the findings of one study, although some statistically significant results were observed (Trim et al. 2021). As a common chronic disease, the relationship between chronic diarrhea and PAEs exposure still needs more research and analysis in the future, as well as its underlying mechanism.

Chronic diarrhea is a common problem in all age groups but poses special challenges in the elderly as a special patient population (Schiller 2019). An increase in body mass index (BMI) is correlated with an elevation in all-cause mortality and diseases associated with higher mortality, including diabetes, cardiovascular disease, and cancer, comprising diseases of the gastrointestinal system. Gastrointestinal symptoms such as vomiting and diarrhea are more common in obese patients than in normal-weight patients (Moayyedi 2008). Obesity increases the risk of various gastrointestinal and liver diseases. Studies have provided strong evidence that in a nationally representative US adult population, obesity is positively associated with chronic diarrhea, and the risk of diarrhea increases with the severity of obesity (Ballou et al. 2019). However, the mechanism of the relationship between obesity and diarrhea still needs to be further explored. Current research points to changes including bile acid absorption and intestinal physiology (increased colonic motility and intestinal permeability). And the link between gut microbiota and this obesity and diarrhea is very likely (Sayuk and Elwing 2019). Bile acid diarrhea is the commonest unexplained cause of chronic diarrhea. Various pathophysiological causes can lead to chronic diarrhea. Even after excluding more common causes, 5% of the population is affected by unexplained chronic diarrhea (Storr et al. 2021). Although the majority of studies have demonstrated decreased diversity and richness of the gut microbiota in obese people, there is still much debate on the actual microbial signature of healthy or obese gut microbiota (Vallianou et al. 2019).

The current study has numerous limitations. Firstly, though the NHANES database comprises sampling weights for facilitating the NHANES sample extrapolation to the general population of the USA, but weighting methods based on selected demographics may still fail to take into account the complex interactions between factors such as race, income level, and BMI. Therefore, the diarrhea patients addressed in this article may not be representative of all people in the USA who suffer from chronic diarrhea. Secondly, NHANES is cross-sectional in nature and hence unable to detect the temporal and causal relation between the onset of chronic diarrhea and exposure to PAEs. Since the NHANES data are based on self-reports, there may be some recall bias when asking about common or most common stool types.

At the same time, the present study has some advantages. First, constipation, as a common disease state, is not easy to assess at a small population level. The study used data from a representative large population survey (NHANES) that included study data from three periods from 2005 to 2010, enabling a relatively accurate assessment of constipation. Secondly, due to the comprehensive nature of the NHANES cohort, we were able to adjust for many of the established risk factors for constipation. To our knowledge,

this study is the first in-depth investigation of the relationship between PAEs and chronic diarrhea. Finally, BKMR can flexibly model exposure to address interactions and nonlinear relationships. In this study, the BKMR model was able to assess the overall relationship between PAEs and chronic diarrhea risk while identifying a single potential interaction.

Conclusion

Mixed exposure to PAEs can promote the occurrence of chronic diarrhea, and the effect was more pronounced in obese people. Notably, most PAEs showed some degree of protection in overweight people. The risk effect of PAEs was more significant in the middle-aged and older population than in the younger population. Future studies should further explore the complex pathophysiological interactions between PAEs exposure, obesity, and intestinal symptoms and their underlying mechanisms.

Declarations

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